

Amendments to the Specification

Please replace the paragraph at page 5, line 26 through page 6, line 11 with the following amended paragraph:

One example of an NPAR agonist is a thrombin peptide derivative and physiologically functional equivalents, i.e., a polypeptide with no more than about fifty amino acids, preferably no more than about thirty amino acids and having sufficient homology to the fragment of human thrombin corresponding to prothrombin amino acids 508-530 (~~SEQ ID NO. 5~~) (SEQ ID NO.:5) that the polypeptide activates NPAR. The thrombin peptide derivatives described herein preferably have between about 12 and 23 amino acids, more preferably between about 19 and 23 amino acids. One example of a thrombin peptide derivative comprises a moiety represented by Structural Formula (I):



(I)

R is a serine esterase conserved domain. Serine esterases, e.g., trypsin, thrombin, chymotrypsin and the like, have a region that is highly conserved. "Serine esterase conserved domain" refers to a polypeptide having the amino acid sequence of one of these conserved regions or is sufficiently homologous to one of these conserved regions such that the thrombin peptide derivative retains NPAR activating ability.

Please replace the paragraph at page 6, lines 12 through 22 with the following amended paragraph:

In one embodiment, the serine esterase conserved sequence has the amino acid sequence of ~~SEQ ID NO. 1~~ SEQ ID NO.:1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val) or a C-terminal truncated fragment of a polypeptide having the amino acid sequence of ~~SEQ ID NO. 1~~ SEQ ID NO.:1. It is understood, however, that zero, one, two or three amino acids in the serine esterase conserved sequence can differ from the corresponding amino acid in ~~SEQ ID NO. 1~~ SEQ ID NO.:1. Preferably, the amino acids in the serine esterase conserved sequence which differ from the corresponding amino acid in ~~SEQ ID NO. 1~~ SEQ ID NO.:1 are conservative substitutions, and are more preferably highly conservative substitutions. A "C-terminal truncated fragment" refers

to a fragment remaining after removing an amino acid or block of amino acids from the C-terminus, said fragment having at least six and more preferably at least nine amino acids.

Please replace the paragraph at page 6, lines 23 through 26 with the following amended paragraph:

More preferably, the serine esterase conserved sequence has the amino acid sequence of ~~SEQ ID NO 2~~ SEQ ID NO.:2 (Cys-X₁-Gly-Asp-Ser-Gly-Gly-Pro-X₂-Val; X₁ is Glu or Gln and X₂ is Phe, Met, Leu, His or Val) or a C-terminal truncated fragment thereof having at least six amino acids, preferably at least nine amino acids.

Please replace the paragraph at page 6, line 27 through page 7, line 14 with the following amended paragraph:

In a preferred embodiment, the thrombin peptide derivative comprises a serine esterase conserved sequence and a polypeptide having a more specific thrombin amino acid sequence Arg-Gly-Asp-Ala (~~SEQ ID NO 3~~) (SEQ ID NO.:3). One example of a thrombin peptide derivative of this type comprises Arg-Gly-Asp-Ala-Cys-X₁-Gly-Asp-Ser-Gly-Gly-Pro-X₂-Val (SEQ ID NO 4). X₁ and X₂ are as defined above. When the thrombin peptide derivative comprises ~~SEQ ID NO 4~~ SEQ ID NO.:4, it preferably has the amino acid sequence of ~~SEQ ID NO 5~~ SEQ ID NO.:5 (Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val) or an N-terminal truncated fragment thereof, provided that zero, one, two or three amino acids at positions 1-9 in the thrombin peptide derivative differ from the amino acid at the corresponding position of ~~SEQ ID NO 5~~ SEQ ID NO.:5. Preferably, the amino acids in the thrombin peptide derivative which differ from the corresponding amino acid in ~~SEQ ID NO 5~~ SEQ ID NO.:5 are conservative substitutions, and are more preferably highly conservative substitutions. An "N-terminal truncated fragment" refers to a fragment remaining after removing an amino acid or block of amino acids from the N-terminus, preferably a block of no more than six amino acids, more preferably a block of no more than three amino acids.

Please replace the paragraph at page 7, lines 15 through 16 with the following amended paragraph:

TP508 is an example of a thrombin peptide derivative and has the amino acid sequence of ~~SEQ ID NO:5~~ SEQ ID NO:5. A physiologically functional equivalent of SEQ ID NO:5 is SEQ ID NO:6 which has the identical amino acid sequence of SEQ ID NO:5 and also contains a C-terminal amide.

Please add the following new paragraphs at page 6, line 12, immediately prior to the paragraph at lines 12 through 22:

A physiologically functional equivalent of a thrombin derivative encompasses molecules which differ from thrombin derivatives in particulars which do not affect the function of the thrombin receptor binding domain or the serine esterase conserved amino acid sequence. Such particulars may include, but are not limited to, conservative amino acid substitutions and modifications, for example, amidation of the carboxyl terminus, acetylation of the amino terminus, conjugation of the polypeptide to a physiologically inert carrier molecule, or sequence alterations in accordance with the serine esterase conserved sequences.

A thrombin receptor binding domain is defined as a polypeptide which directly binds to the thrombin receptor and/or competitively inhibits binding between high-affinity thrombin receptors and alpha thrombin.